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L3 ANSWER 1 OF 2 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 144:292785 CASREACT
TITLE: Process for preparation of 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine (Quetiapine) from 2-amino-2'-carboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine.
INVENTOR(S): Pathak, Shailendra; Sharma, Jitendra; Kaushik, Geetesh; Thaper, Rajesh Kumar; Dubey, Sushil Kumar
PATENT ASSIGNEE(S): Jubilant Organosys Limited, India
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006027789	A1	20060316	WO 2004-IN281	20040908
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
IN 2006DN04348	A	20070713	IN 2006-DN4348	20060727

PRIORITY APPLN. INFO.: WO 2004-IN281 20040908
AN 144:292785 CASREACT
TI Process for preparation of 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine (Quetiapine) from 2-amino-2'-carboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine.
IN Pathak, Shailendra; Sharma, Jitendra; Kaushik, Geetesh; Thaper, Rajesh Kumar; Dubey, Sushil Kumar
PA Jubilant Organosys Limited, India
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D281-02
CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2006027789	A1	20060316	WO 2004-IN281	20040908
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI,				

CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

IN 2006DN04348 A 20070713 IN 2006-DN4348 20060727

PRAI WO 2004-IN281 20040908

AB A process for preparation of Quetiapine comprises reaction of 2-amino-2'-carboxydiphenyl sulfide with a phosphorus halide or oxyhalide to give an iminohalide which is treated with 1-hydroxyethoxyethylpiperazine.

ST Quetiapine prepn; dibenzothiazepinylpiperazinylethoxyethanol prepn; aminocarboxydiphenyl sulfide hydroxyethoxyethylpiperazine reaction

IT Bases, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(inorg.; preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)

IT Bases, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(organic; preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)

IT Phase transfer catalysts
(preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)

IT Bicarbonates
Carbonates, reactions
Hydrides
Hydroxides (inorganic)
Metal alkoxides
RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)

IT 5747-48-8P 19806-43-0P 329216-67-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)

IT 111974-69-7P, Quetiapine 111974-72-2P, Quetiapine hemifumarate
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)

IT 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 67-64-1, Acetone, uses 67-68-5, Dimethyl sulfoxide, uses 68-12-2, Dmf, uses 80-73-9 120-94-5, N-Methylpyrrolidine 127-19-5, Dimethylacetamide 141-78-6, Ethyl acetate, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)

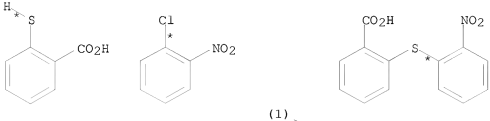
IT 88-73-3, o-Chloronitrobenzene 103-76-4, 1-(2-Hydroxyethyl)piperazine 107-21-1, Ethylene glycol, reactions 110-85-0, Piperazine, reactions 147-93-3, 2-Mercaptobenzoic acid 577-19-5, o-Bromonitrobenzene 609-73-4, o-Iodonitrobenzene 1493-27-2, o-Fluoronitrobenzene 13349-82-1 54920-98-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Quetiapine from aminocarboxydiphenyl sulfide and 1-hydroxyethoxyethylpiperazine)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Ici Americas Inc; EP 0240228 A1 1987 CAPLUS

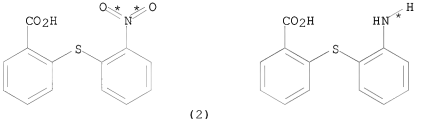
RX(1) OF 20 A + B ===> C...



A B C

RX(1) RCT A 147-93-3, B 88-73-3
RGT D 584-08-7 K2CO3
PRO C 19806-43-0
CAT 311-28-4 Bu4N.I
SOL 67-56-1 MeOH
CON 4 - 6 hours, room temperature -> 70 deg C

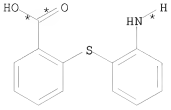
RX(2) OF 20 ...C ===> G...



C G

RX(2) RCT C 19806-43-0
RGT H 1333-74-0 H2
PRO G 54920-98-8
CAT 7440-05-3 Pd
SOL 67-56-1 MeOH
CON 10 - 15 hours, 30 - 35 deg C, 100 psi

RX(3) OF 20 ...G + J ===> K



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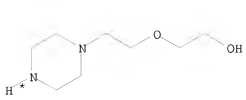

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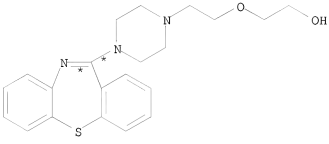


K

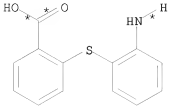
RX(3) RCT G 54920-98-8

STAGE(1)
SOL 10025-87-3 POC13
CON 5 - 6 hours, room temperature -> 110 deg C

STAGE(2)
RCT J 13349-82-1
RGT L 497-19-8 Na2CO3
SOL 108-88-3 PhMe, 872-50-4 NMEP
CON SUBSTAGE(2) 6 - 8 hours, reflux

PRO K 111974-69-7

RX(4) OF 20 ...G + P ===> Q...



G

P

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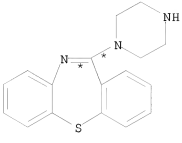


Q

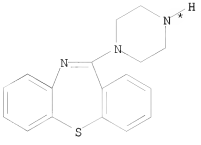
RX(4) RCT G 54920-98-8

STAGE(1)
SOL 10025-87-3 POCl3
CON 5 - 6 hours, room temperature -> 110 deg C

STAGE(2)
RCT P 110-85-0
SOL 108-88-3 PhMe
CON SUBSTAGE(1) 110 - 120 deg C
SUBSTAGE(2) 6 - 8 hours

PRO Q 5747-48-8

RX(5) OF 20 ...Q + R ===> K



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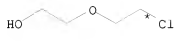

R

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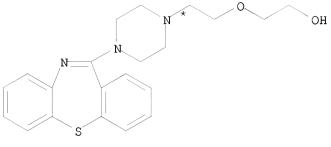
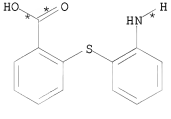


K

RX(5) RCT Q 5747-48-8, R 628-89-7
RGT L 497-19-8 Na2CO3
PRO K 111974-69-7
SOL 71-36-3 BuOH
CON 10 - 12 hours, room temperature -> 120 deg C

RX(6) OF 20 ...G + J ===> T...



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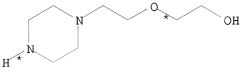

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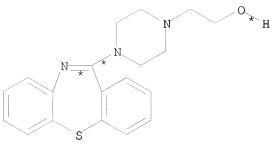


T

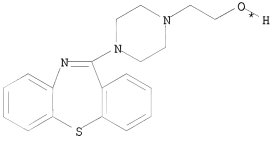
RX(6) RCT G 54920-98-8

STAGE(1)
RGT M 10025-87-3 POC13
SOL 108-88-3 PhMe
CON 5 - 6 hours, room temperature -> 110 deg C

STAGE(2)
RCT J 13349-82-1
SOL 108-88-3 PhMe, 872-50-4 NMEP
CON SUBSTAGE(2) 6 - 8 hours, 110 - 120 deg C

PRO T 329216-67-3

RX(7) OF 20 ...T + U ===> K



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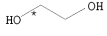

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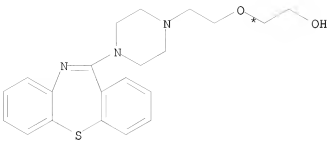

K

RX(7) RCT T 329216-67-3

STAGE(1)
RGT V 121-44-8 Et3N, W 124-63-0 MeSO2Cl
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(3) 2 hours, room temperature

STAGE(2)
RCT U 107-21-1
RGT X 7646-69-7 NaH
SOL 107-21-1 (CH2OH)2, 108-88-3 PhMe
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 10 - 12 hours, room temperature -> 120 deg C

PRO K 111974-69-7

L3 ANSWER 2 OF 2 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 142:240472 CASREACT
TITLE: Procedure for preparing a pharmaceutically active compound
INVENTOR(S): Puig Torres, Salvador; Herbera Espinal, Reyes; Dalmases Barjoan, Pere
PATENT ASSIGNEE(S): Laboratorios Vita, S. A., Spain
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005014590	A2	20050217	WO 2004-IB2527	20040727
WO 2005014590	A3	20050506		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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ES 2223294	B2	20051001		
EP 1660468	A2	20060531	EP 2004-744176	20040727
EP 1660468	B1	20070718		
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AT 367383	T	20070815	AT 2004-744176	20040727
ES 2290734	T3	20080216	ES 2004-744176	20040727
US 20060189594	A1	20060824	US 2006-566413	20060130

PRIORITY APPLN. INFO.: ES 2003-1922 20030808
WO 2004-IB2527 20040727

OTHER SOURCE(S): MARPAT 142:240472
AN 142:240472 CASREACT
TI Procedure for preparing a pharmaceutically active compound
IN Puig Torres, Salvador; Herbera Espinal, Reyes; Dalmases Barjoan, Pere
PA Laboratorios Vita, S. A., Spain
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D417-00
CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005014590	A2	20050217	WO 2004-IB2527	20040727
	WO 2005014590	A3	20050506		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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ES 2223294 A1 20050216 ES 2003-1922 20030808
ES 2223294 B2 20051001
EP 1660468 A2 20060531 EP 2004-744176 20040727
EP 1660468 B1 20070718
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JP 2007501837 T 20070201 JP 2006-523068 20040727
AT 367383 T 20070815 AT 2004-744176 20040727
ES 2290734 T3 20080216 ES 2004-744176 20040727
US 20060189594 A1 20060824 US 2006-566413 20060130
PRAI ES 2003-1922 20030808
WO 2004-IB2527 20040727
OS MARPAT 142:240472
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a procedure for preparing quetiapine (I) by reaction between dibenzothiazepine II and a compound P-OCH2CH2X [P = alc. protective group resistant to alkaline conditions; especially ethers, e.g., tetrahydropyranyl, CH2Ph, trityl; X = leaving group, e.g., halogen, mesylate, triflate, nonaflate, tresylate, tosylate, brosylate, nosylate], in the presence of a base, followed by a step of deprotection of ether III and, optionally, obtaining a pharmaceutically acceptable salt thereof. Said procedure permits the obtaining of quetiapine with a high degree of purity under soft temperature conditions, with short reaction times and avoiding the use of toxic solvents.

ST quetiapine prepn; dibenzothiazepine hydroxyethylpiperazino etherification

IT Hydrolysis
(acid, of O-protected quetiapine; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)

IT Bases, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(alkali and alkaline earth metal derivs.; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)

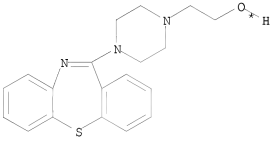
IT Carbonates, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(alkali metal and alkaline earth derivs.; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)

IT Heterocyclic compounds
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

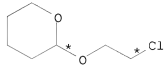
(dibenzothiazepines; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT Protective groups
(ethers, alkaline resistant; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT Phase transfer catalysts
(for etherification of a dibenzothiazepine piperazinoethanol derivative; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT Etherification
(of a dibenzothiazepine piperazinoethanol derivative; procedure for preparing
quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT Alkali metal hydroxides
Alkaline earth hydroxides
RL: RGT (Reagent); RACT (Reactant or reagent)
(procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT Quaternary ammonium compounds, uses
RL: CAT (Catalyst use); USES (Uses)
(tri-C8-10-alkylmethyl, chlorides, for etherification of a dibenzothiazepine piperazinoethanol derivative; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT 1310-58-3, Potassium hydroxide, reactions 1310-73-2, Sodium hydroxide, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(etherification agent; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT 1235-23-0, 2-Chloroethyl trityl ether 5631-96-9, 2-(2-Chloroethoxy)-2H-tetrahydropyran 17229-17-3, Benzyl 2-chloroethyl ether 65338-95-6, 2-[(Tetrahydropyran-2-yl)oxy]ethyl p-toluenesulfonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(etherification by, of dibenzothiazepine piperazinoethanol derivative; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT 329216-67-3, 2-[4-(Dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(etherification of, with (chloroethoxy)tetrahydropyran and analogs; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT 311-28-4, Tetrabutylammonium iodide 17455-13-9, 18-Crown-6 32503-27-8, Tetrabutylammonium bisulfate
RL: CAT (Catalyst use); USES (Uses)
(phase-transfer catalyst; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT 844639-08-3P, 11-[4-[2-(2-Benzyloxyethoxy)ethyl]piperazin-1-yl]dibenzo[b,f][a,4]thiazepine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and acetolysis of; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT 844639-08-1P, 11-[4-[2-(2-Trityloxyethoxy)ethyl]piperazin-1-yl]dibenzo[b,f][a,4]thiazepine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and acid hydrolysis of; procedure for preparing quetiapine from a

dibenzothiazepine piperazinoethanol derivative)
IT 844639-07-2P, 11-[4-[2-(2-Acetoxyethoxy)ethyl]piperazin-1-yl]dibenzo[b,f][a,4]thiazepine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and basic hydrolysis of; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT 111974-69-7P, Quetiapine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with fumaric acid; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT 111974-72-2P, Quetiapine hemifumarate
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and reaction of, with fumaric acid; procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)
IT 110-17-8, Fumaric acid, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(procedure for preparing quetiapine from a dibenzothiazepine piperazinoethanol derivative)

RX(1) OF 13 A + B ===> C

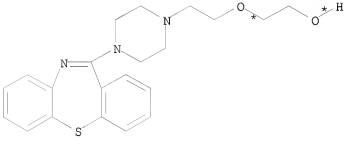


A



B

(1)



C
YIELD 85%

RX(1)

STAGE(1)
RGT D 1310-73-2 NaOH
SOL 7732-18-5 Water
CON 25 deg C

STAGE(2)
RCT A 329216-67-3
CON 25 deg C

STAGE(3)
RCT B 5631-96-9
CON 25 deg C

STAGE(4)
CAT 32503-27-8 Bu4N.HSO4
CON SUBSTAGE(1) 25 deg C
SUBSTAGE(2) 25 deg C -> 60 deg C
SUBSTAGE(3) 6 hours, 60 deg C
SUBSTAGE(4) 60 deg C -> 20 deg C

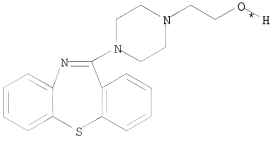
STAGE(5)
SOL 7732-18-5 Water, 108-88-3 PhMe
CON 20 - 25 deg C

STAGE(6)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water
CON 3 hours, 20 - 25 deg C

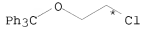
STAGE(7)
RGT F 584-08-7 K2CO3
SOL 7732-18-5 Water
CON 20 - 25 deg C, pH 10

PRO C 111974-69-7

RX(2) OF 13 A + J ===> K...

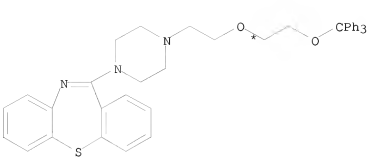


A



J

(2)



K
YIELD 82%

RX(2) RCT A 329216-67-3, J 1235-23-0

STAGE(1)
CON 100 - 110 deg C

STAGE(2)
RGT L 1310-58-3 KOH
CON 45 - 60 minutes, 100 - 110 deg C

STAGE(3)
CAT 17455-13-9 18-Crown-6
CON 2 hours, 100 - 110 deg C

STAGE(4)
SOL 108-88-3 PhMe
CON 100 - 110 deg C

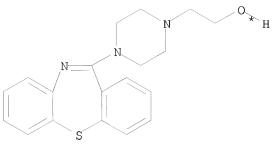
STAGE(5)
SOL 7732-18-5 Water
CON 100 - 110 deg C -> 20 deg C

STAGE(6)
SOL 67-56-1 MeOH, 108-88-3 PhMe
CON SUBSTAGE(1) 35 - 40 deg C
SUBSTAGE(2) 35 - 40 deg C -> 0 deg C

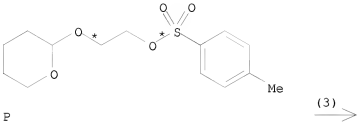
STAGE(7)
SOL 67-56-1 MeOH, 78-93-3 EtCOMe
CON SUBSTAGE(1) reflux
SUBSTAGE(2) reflux -> 20 deg C
SUBSTAGE(3) 1 hour, 20 - 25 deg C
SUBSTAGE(4) 20 - 25 deg C -> 0 deg C

PRO K 844639-06-1
NTE first stage fusion; fifth stage crystn.; last stage recrystn.

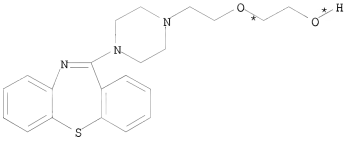
RX(3) OF 13 A + P ===> C



A



P



C
YIELD 90%

RX(3)

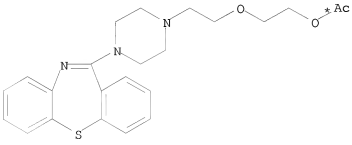
STAGE(1)
RGT D 1310-73-2 NaOH
SOL 7732-18-5 Water
CON 25 deg C

STAGE(2)
RCT A 329216-67-3
CON 25 deg C

STAGE(3)

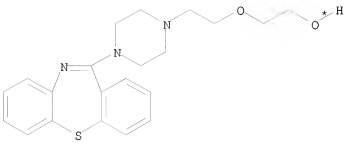
```
               RCT  P 65338-95-6
               CON  25 deg C

            STAGE(4)
               CAT  32503-27-8 Bu4N.HSO4
               CON  SUBSTAGE(1) 25 deg C
                    SUBSTAGE(2) 25 deg C -> 60 deg C
                    SUBSTAGE(3) 8 hours, 60 - 65 deg C
                    SUBSTAGE(4) 60 - 65 deg C -> 20 deg C

            STAGE(5)
               SOL  7732-18-5 Water, 108-88-3 PhMe
               CON  20 - 25 deg C

            STAGE(6)
               RGT  E 7647-01-0 HCl
               SOL  7732-18-5 Water
               CON  3 hours, 20 - 25 deg C

            STAGE(7)
               RGT  F 584-08-7 K2CO3
               SOL  7732-18-5 Water
               CON  20 - 25 deg C, pH 10

          PRO  C 111974-69-7
```

RX(4) OF 13 ...Q ===> C



Q

(4)



C
YIELD 94%

RX(4) RCT Q 844639-07-2

STAGE(1)
SOL 67-56-1 MeOH
CON 20 - 25 deg C

STAGE(2)
RGT L 1310-58-3 KOH
CON 3 hours, 20 - 25 deg C

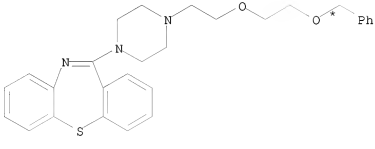
STAGE(3)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water
CON 20 - 25 deg C

STAGE(4)
RGT D 1310-73-2 NaOH
SOL 7732-18-5 Water
CON 20 - 25 deg C, pH 10

PRO C 111974-69-7

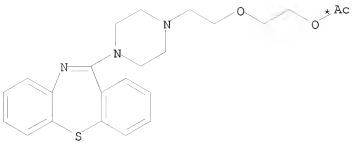
RX(5) OF 13 ...R + S ===> Q...

R



S

(5)



Q
YIELD 89%

RX(5) RCT R 64-19-7

STAGE(1)
RGT T 10035-10-6 HBr
SOL 64-19-7 AcOH
CON 20 - 25 deg C

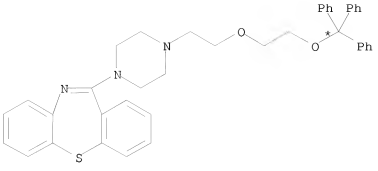
STAGE(2)
RCT S 844639-08-3
CON 1.5 hours, 20 - 25 deg C

STAGE(3)
SOL 7732-18-5 Water, 75-09-2 CH2Cl2
CON 20 - 25 deg C

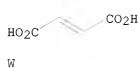
STAGE(4)
RGT U 144-55-8 NaHCO3
CON 20 - 25 deg C

PRO Q 844639-07-2
NTE last stage neutralization

RX(6) OF 13 ...K + W ===> X



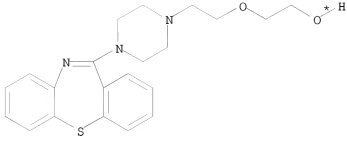
K



W

(6)

X: CM 1



X: CM 2

RX(6) RCT K 844639-06-1

STAGE(1)
CAT 104-15-4 TsOH
SOL 67-56-1 MeOH, 108-88-3 PhMe
CON 4 hours, reflux

STAGE(2)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water, 108-88-3 PhMe
CON 20 - 25 deg C

STAGE(3)
RGT D 1310-73-2 NaOH
SOL 7732-18-5 Water, 108-88-3 PhMe
CON 20 - 25 deg C, pH 9.5

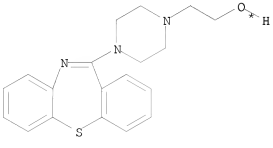
STAGE(4)
SOL 67-56-1 MeOH

CON 20 - 25 deg C

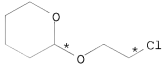
STAGE(5)
RCT W 110-17-8
CON SUBSTAGE(1) 35 - 45 minutes, 20 - 25 deg C
SUBSTAGE(2) 20 - 25 deg C -> reflux
SUBSTAGE(3) 5 minutes, reflux
SUBSTAGE(4) reflux -> 10 deg C
SUBSTAGE(5) 1 hour, 10 - 15 deg C

PRO X 111974-72-2
NTE (95%;94%)

RX(7) OF 13 A + B ===> C

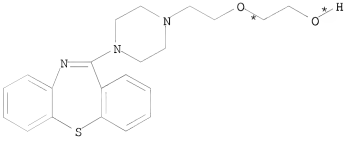


A



B

(7)



C
YIELD 82%

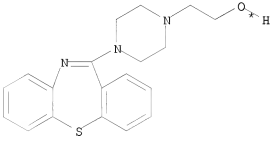
RX(7)

STAGE(1)
RGT L 1310-58-3 KOH
SOL 7732-18-5 Water
CON 25 deg C

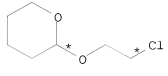
STAGE(2)

```
      RCT  A 329216-67-3
      CON  25 deg C

   STAGE(3)
      RCT  B 5631-96-9
      CON  25 deg C

   STAGE(4)
      CAT  17455-13-9 18-Crown-6
      CON  SUBSTAGE(1) 25 deg C
           SUBSTAGE(2) 25 deg C -> 40 deg C
           SUBSTAGE(3) 6 hours, 40 deg C
           SUBSTAGE(4) 40 deg C -> 20 deg C

   STAGE(5)
      SOL  7732-18-5 Water, 108-88-3 PhMe
      CON  20 - 25 deg C

   STAGE(6)
      RGT  E 7647-01-0 HCl
      SOL  7732-18-5 Water
      CON  3 hours, 20 - 25 deg C

   STAGE(7)
      RGT  F 584-08-7 K2CO3
      SOL  7732-18-5 Water
      CON  20 - 25 deg C, pH 10

PRO  C 111974-69-7
```

RX(8) OF 13 A + B ===> C

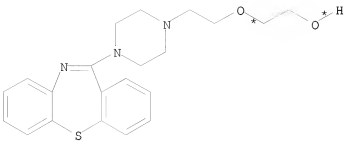


A



B

(8)



C
YIELD 75%

RX(8)

STAGE(1)
RGT L 1310-58-3 KOH
SOL 7732-18-5 Water
CON 25 deg C

STAGE(2)
RCT A 329216-67-3
CON 25 deg C

STAGE(3)
RCT B 5631-96-9
CON 25 deg C

STAGE(4)
CON SUBSTAGE(1) 25 deg C
SUBSTAGE(2) 25 deg C -> 40 deg C
SUBSTAGE(3) 20 hours, 40 deg C
SUBSTAGE(4) 40 deg C -> 20 deg C

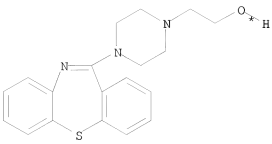
STAGE(5)
SOL 7732-18-5 Water, 108-88-3 PhMe
CON 20 - 25 deg C

STAGE(6)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water
CON 3 hours, 20 - 25 deg C

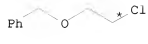
STAGE(7)
RGT F 584-08-7 K2CO3
SOL 7732-18-5 Water
CON 20 - 25 deg C, pH 10

PRO C 111974-69-7
NTE stage 4 Aliquat 336 catalyst

RX(9) OF 13 A + Z ===> S...

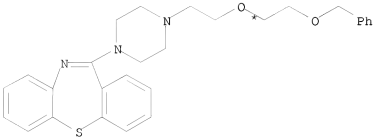


A



Z

(9)



S
YIELD 93%

RX(9)

```
STAGE(1)
   RGT  D 1310-73-2 NaOH
   SOL  7732-18-5 Water
   CON  20 - 25 deg C

STAGE(2)
   RCT  A 329216-67-3
   CON  20 - 25 deg C

STAGE(3)
   RCT  Z 17229-17-3
   CON  20 - 25 deg C

STAGE(4)
   CAT  32503-27-8 Bu4N.HSO4
   CON  SUBSTAGE(1) 20 - 25 deg C
        SUBSTAGE(2) 20 - 25 deg C -> 60 deg C
        SUBSTAGE(3) 9 hours, 60 deg C
        SUBSTAGE(4) 60 deg C -> 20 deg C

STAGE(5)
```

```
      SOL  7732-18-5 Water, 108-88-3 PhMe
      CON  20 - 25 deg C

   STAGE(6)
      RGT  E 7647-01-0 HCl
      SOL  7732-18-5 Water
      CON  5 minutes, 20 - 25 deg C

PRO  S 844639-08-3
```